THE SYNTHESIS OF SOME COMPOUNDS STRUCTURALLY RELATED TO COLCHINOL METHYL ETHER

by

ALLAN STUART HAY
B.Sc.

THE UNIVERSITY OF ALBERTA

THE SYNTHESIS OF SOME COMPOUNDS STRUCTURALLY RELATED TO COLCHINOL METHYL ETHER

A DISSERTATION

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

FACULTY OF ARTS AND SCIENCE

DEPARTMENT OF CHEMISTRY

by

ALLAN STUART HAY
B.Sc.

EDMONTON, ALBERTA

April, 1952.

ABSTRACT

Some compounds structurally related to colchinol methyl ether have been synthesized. These compounds are 1-(3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine hydrochloride, N-acetyl-1-(3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine, N-acetyl-1-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine and 1-(3-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine.

The reduction of 3,4,5-trimethoxybenzaldoxime by various reducing agents has been studied.

ACKNOWLEDGMENTS

The author is deeply indebted to Dr. R.B. Sandin, under whose direction he had the privilege of doing this work.

He wishes to thank all the members of the Department of Chemistry and his co-workers for their willing cooperation and assistance whenever needed.

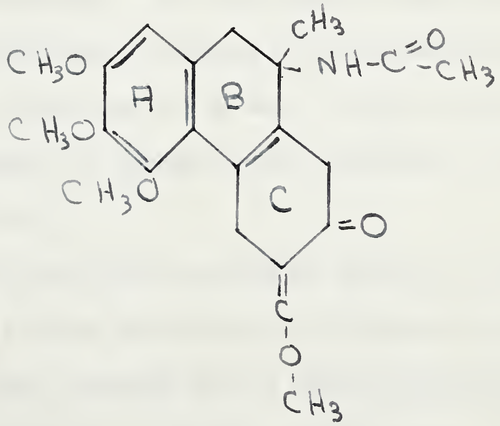
He wishes to thank also the National Cancer Institute for grants which enabled him to carry on this work during the summer months.

INTRODUCTION

Colchicine is an alkaloid obtained from the seeds and corms of the autumn crocus. It is a capillary poison and large doses of it produce paralysis of the nervous system along with respiratory paralysis. For as yet unexplained reasons it also gives relief to those suffering from gout.

The fact that colchicine inhibits cell division (1) led to its testing in the regression of tumours. At doses just sufficient to arrest cell division little effect on the growth of the tumour is discerned (2). Dosages just below the minimum lethal dose are necessary before any regression of tumour growth is noticed. At such high dose levels, however, hemorrhages are induced in the tumour and thus regression may be due to the destruction of the newly formed capillary endothelium in the tumours.

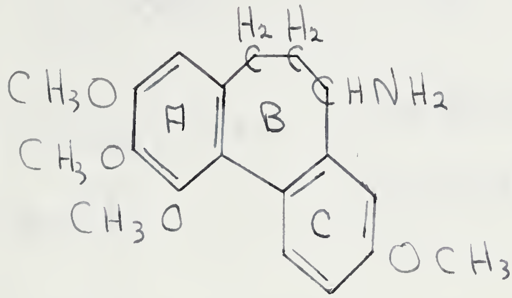
Windaus (3) was the first to partially elucidate the structure for colchicine. He proposed formula I for it.



I

Work by J.W. Cook (4) et al showed that a revision of this

formula was necessary. Their work seemed to indicate that ring B in the Windaus formula (I) should be seven-membered and not six-membered. This would give the following structure for colchinol methyl ether, an important degradation product of colchicine.



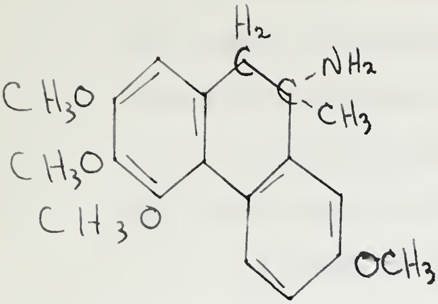
This structure has recently been verified by synthesis (5).

The structure for colchicine itself has not, to date, been completely elucidated. Dewar (6) proposed that rings B and C are both seven-membered. This has received some support (4e,7).

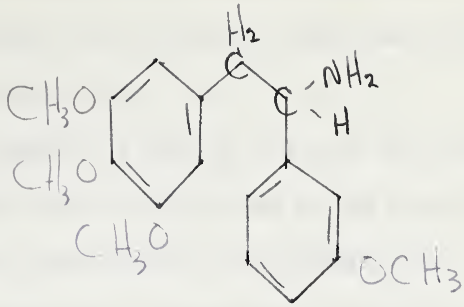
Lettré and co-workers (8) reported that certain 1,2-diphenylethylamines containing one or more methoxyl groups on one of the rings had the property of inhibiting cell division in certain cells in tissue cultures.

This work was extended by Hartwell and Kornberg (9) who synthesized further substituted 1,2-diphenylethylamines.

These compounds bear a close structural relationship to the Windaus structure for colchinol methyl ether as illustrated by the following formulae.

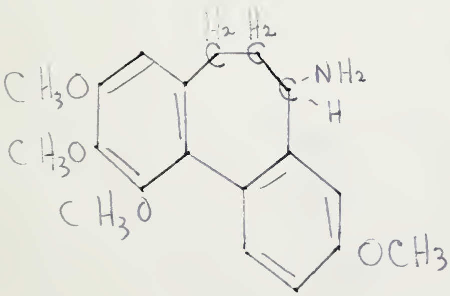


Colchinol Methyl Ether (Windaus)



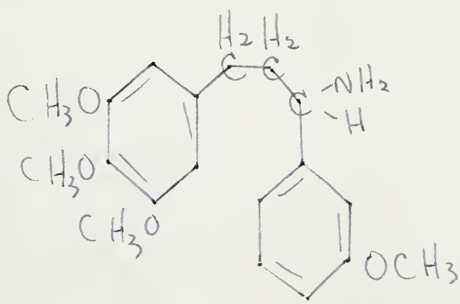
1-(3-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-ethylamine

Since colchinol methyl ether has been shown to contain a seven-membered ring, it is obvious that the best open chain analogue of colchinol methyl ether would be an appropriately substituted 1,3-diphenylpropylamine (III).



Colchinol Methyl Ether

II



1-(3-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine

III

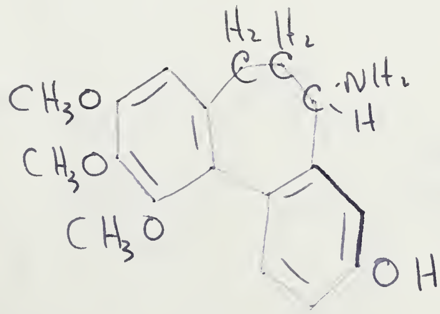
Certain of these substituted 1,3-diphenylpropylamines have been prepared by previous workers (10) and some of these have proved to have mild inhibitory properties (11).

It was proposed to prepare as part of the work involved in this thesis, compound III which was to be isolated as the hydrochloride.

A recent and private communication from Hartwell (11) at the National Cancer Institute has revealed that certain degredation products of colchicine possess inhibitory properties and are less toxic than the parent compound. That is, the maximum tolerated dose (MTD) is much greater than the minimum effective dose (MED) as shown by the following table.

	$\frac{\text{MTD}}{\text{MED}}$
Colchinol	4
Colchinol methyl ether	2
N-acetyl colchinol	30
N-acetyl colchinol methyl ether	7

These results indicate that the presence of an hydroxyl group as in colchinol (IV),

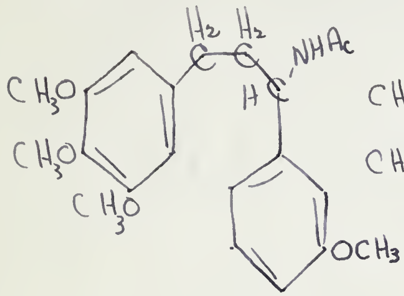


IV

instead of the methoxyl group in colchinol methyl ether (II), plus

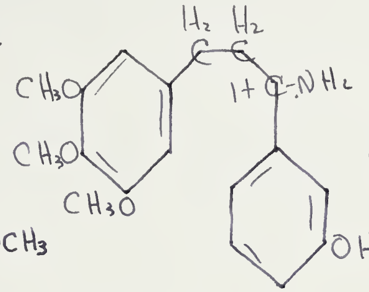
N-acetylation increases the potency of the compounds tremendously.

Accordingly it was proposed that the following compounds, open chain analogues of colchinol and colchinol methyl ether, be prepared.



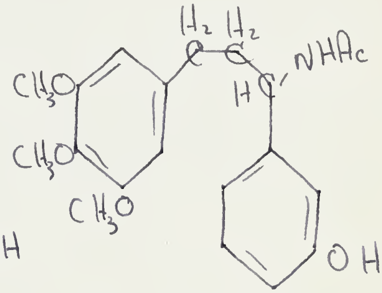
N-Acetyl-1-(3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine.

V



1-(3-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine.

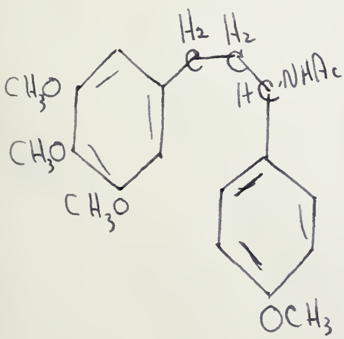
VI



N-Acetyl-(3-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine.

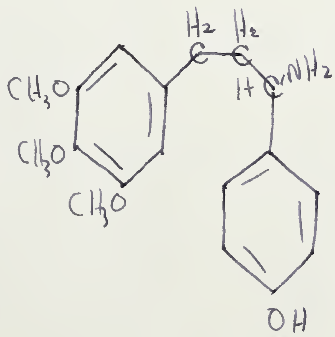
VII

Also as a matter of interest it was suggested that the following be synthesized.



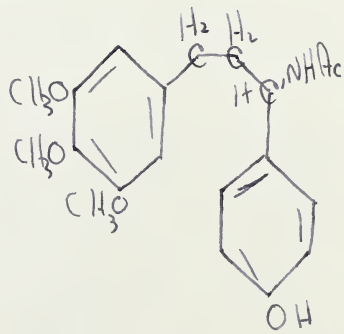
N-Acetyl-1-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine

VIII



1-(4-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine.

IX



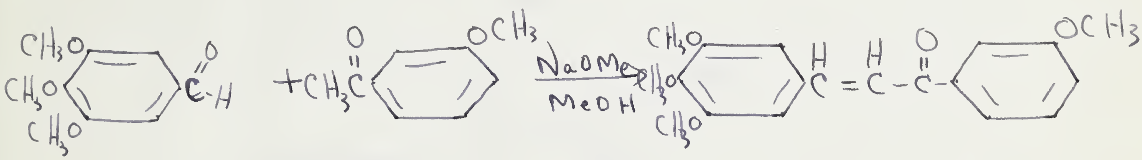
N-Acetyl-1-(4-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine.

X

None of these compounds has been synthesized previously, but the hydrochloride corresponding to compound VIII has been prepared by an earlier worker (10a).

DISCUSSION

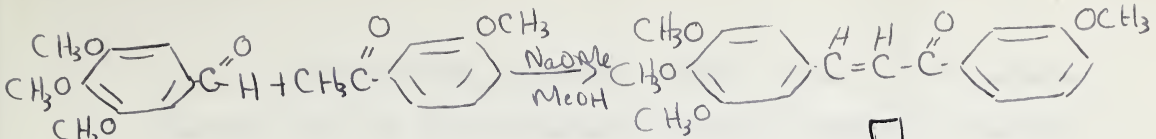
Following a general procedure used by previous workers (10) for the preparation of substituted 1,3-diphenylpropylamines, one would expect the first step in the synthesis of 1-(3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine (I) to be



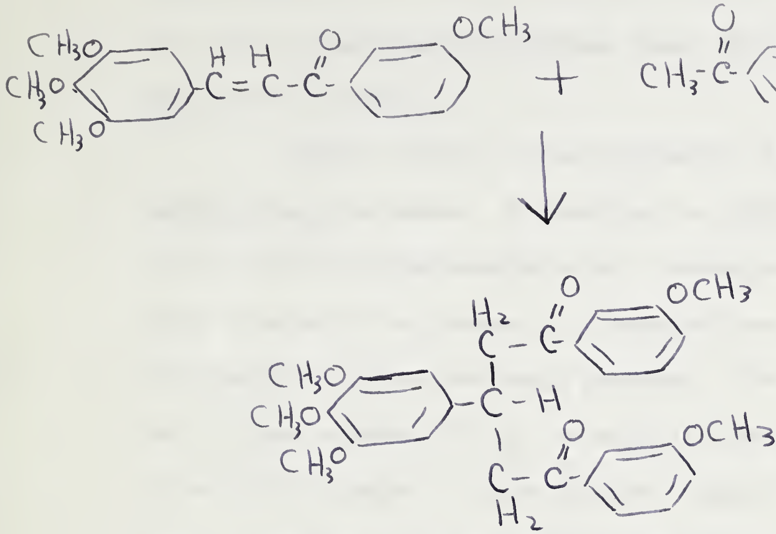
The chalcones produced are generally yellow, and melt at a relatively low temperature. From the above reaction, after prolonged standing, two compounds were isolated. They were both white and melted at approximately 140°C and 170°C, respectively, which is considerably higher than might be expected for the expected chalcone.

The reaction between benzaldehyde and acetophenone has been studied (12) and found to give higher condensation products. Furthermore chalcone itself has been found to react further (13) with acetophenone to give the same higher condensation products via a Michael condensation.

By analogy one would therefore expect the following reactions to occur with 3,4,5-trimethoxybenzaldehyde and methoxyacetophenone.



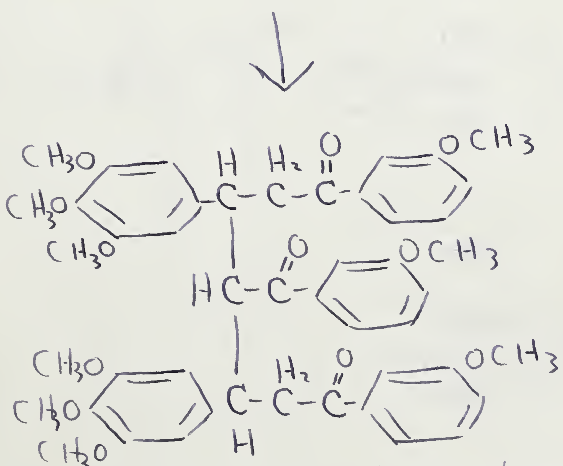
A



3,4,5-Trimethoxybenzylidene-di-(3-methoxyacetophenone)

I

A + I



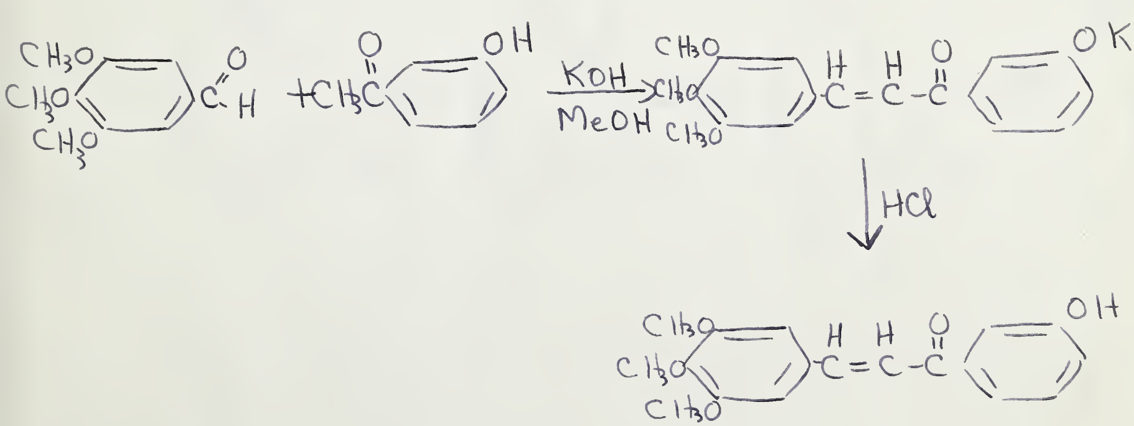
Di-(3,4,5-Trimethoxybenzal)-tris-(3-methoxyacetophenone)

II

Unfortunately, compounds I and II, as well as the expected chalcone, have the same percentages of carbon, hydrogen, and oxygen within experimental error. Therefore a carbon-hydrogen analysis does not serve to differentiate between them. Work on these compounds was not pursured further.

Another worker in this laboratory (13) has done further work on these compounds. By reacting the stoichometric quantities of 3,4,5-trimethoxybenzaldehyde and 3-methoxyacetophenone which might be expected to produce I, a compound was produced which was different from those previously produced. The compound proved to be I. Since compound II has two similar asymmetric carbon atoms, it would be expected to exist in three isomeric forms, d, l, and meso. Therefore, the two compounds produced are probably isomeric forms of II.

Wacek and Morghen (14) reported that chalcones containing a phenolic hydroxyl group could be boiled in alkali without producing higher condensation products. This prompted the following reaction:

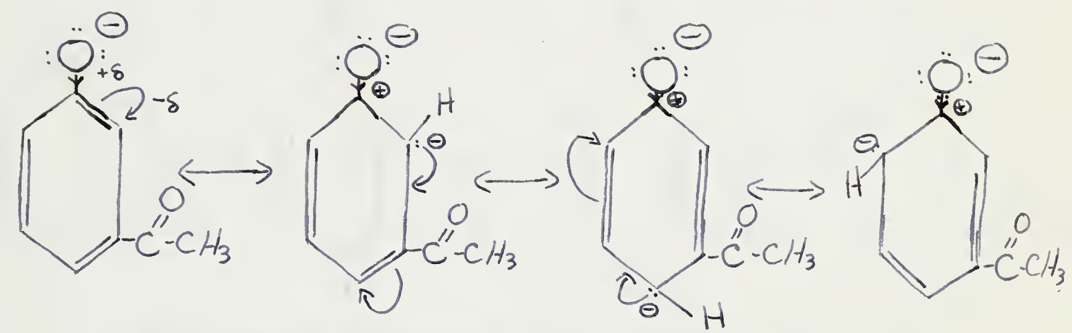


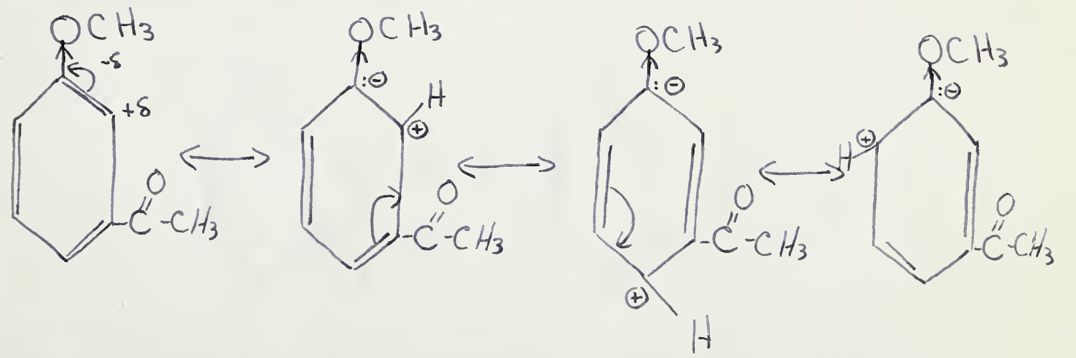
This compound could be prepared in excellent yield.

A search of the literature revealed that no chalcones have been synthesized with methoxyl group in the B ring at the 3' position.

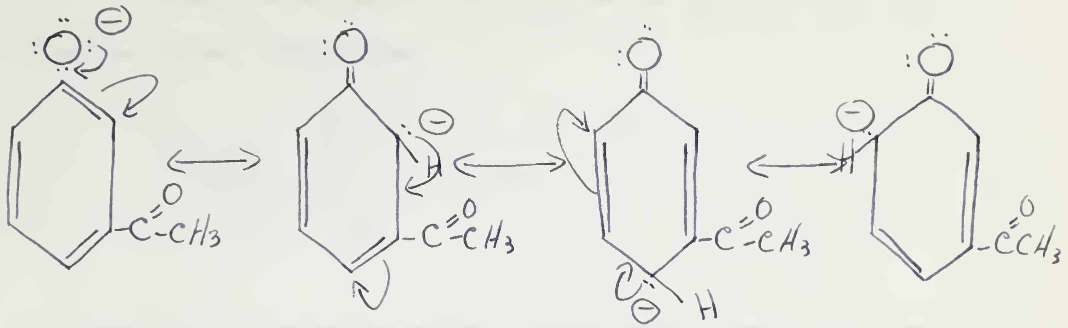
To understand why one compound undergoes a further Michael condensation one must go into the inductive and resonance effects produced by the phenolate ion and methoxyl group respectively.

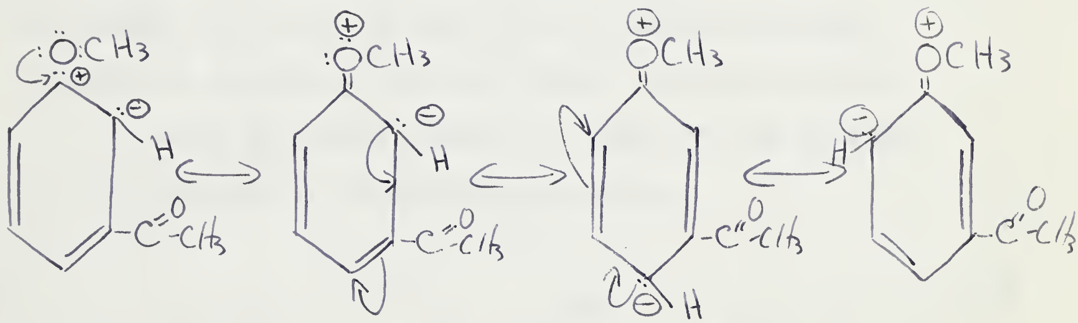
Inductive Effect



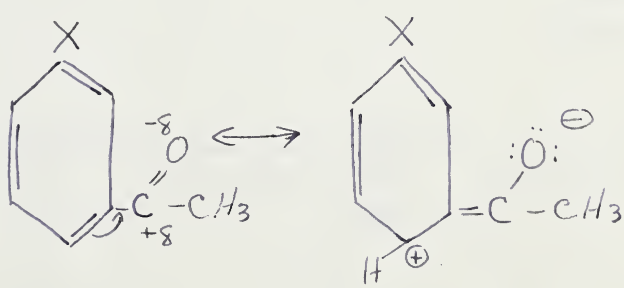


Resonance Effect





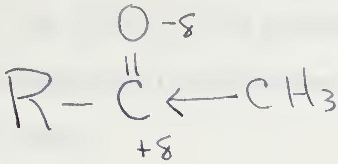
The unhindered polarization of the carbonyl group in the molecule would produce the following effect:



When X is a phenolate ion, both the inductive and resonance effects oppose this polarization of the carbonyl, whereas, when X is a methoxyl the inductive effect aids, the resonance effect hinders the polarization. The directing influence of the phenolate ion is also greater than that of the methoxyl, therefore, the hindrance of polarization of the carbonyl by the other group is greater when that group is a phenolate

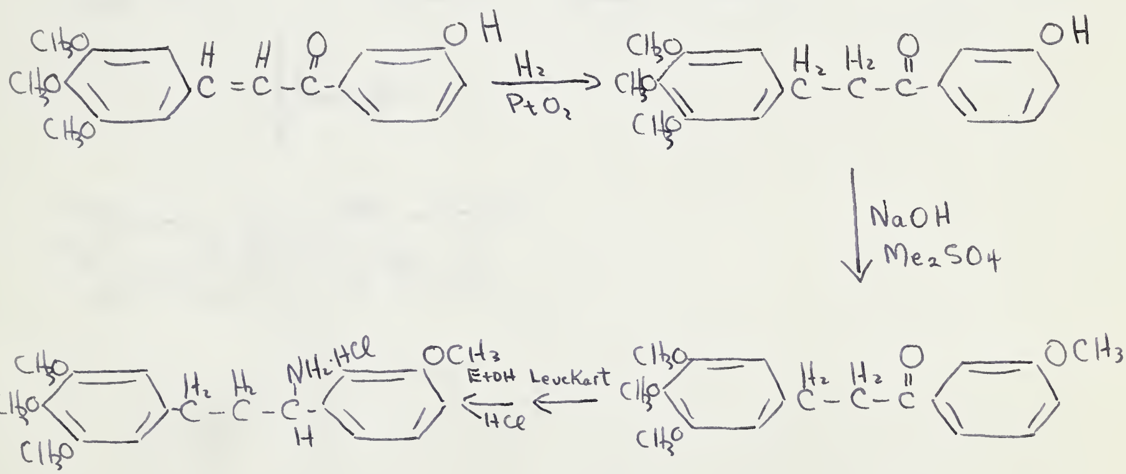
ion.

Since the carbonyl carbon will now be less positive, the inductive effect will be less



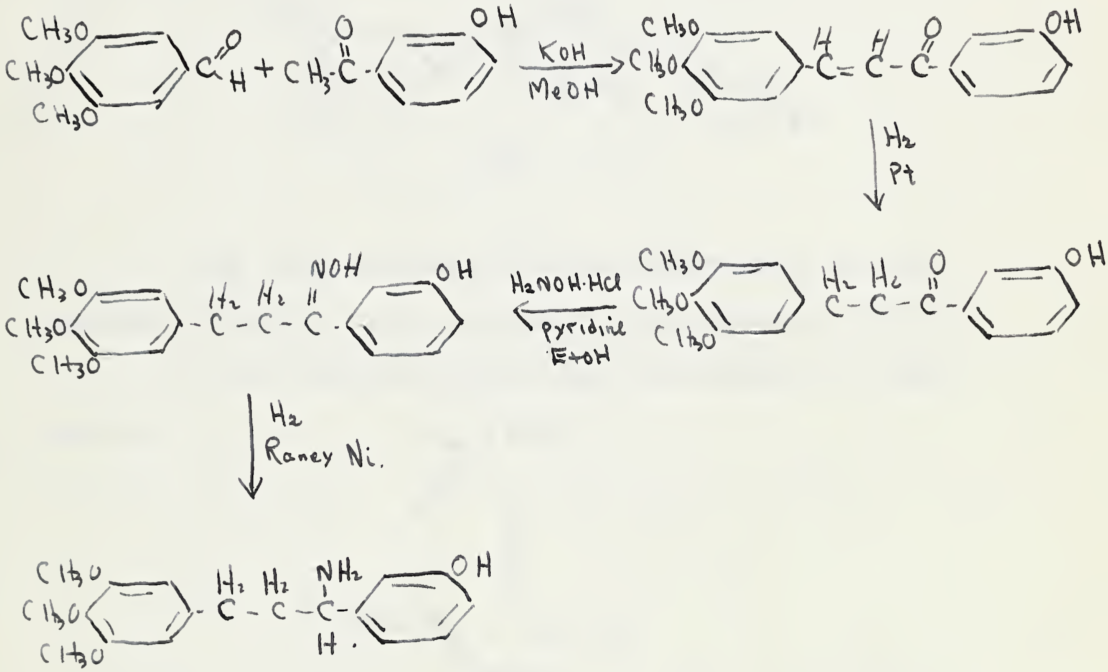
prominent and the hydrogens on the adjacent methyl group will then be less positive than when a methoxyl group is in the ring. This would mean that it would be less likely to undergo the Michael reaction and so would not give the further condensation products.

Using the hydroxy chalcone the scheme for the synthesis of I is illustrated by the following flow sheet.

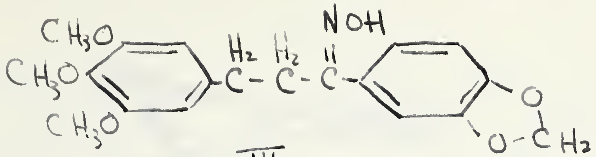


The synthesis of any of the propylamines containing an hydroxyl required a different procedure because the Leuckart reaction is unsuccessful with phenols (15) producing higher condensation products. Sodium amalgam reduction of the oxime of the corresponding

hydrochalcone produced a small yield of the amine. The most successful method was found to be reduction with hydrogen and Raney nickel at 1000 psi and 85° (16) for one hour. This produced an excellent yield of the amine. The route for the synthesis of 1-(3-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine would be illustrated by the following flow sheet.

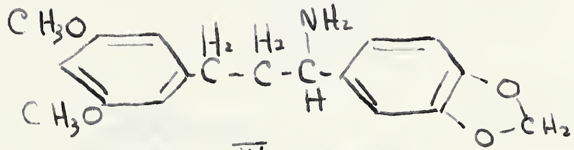


The reduction by previous workers (17) of III by means of



III

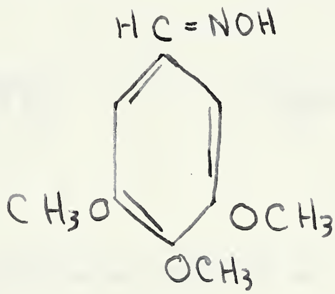
sodium in absolute ethanol gave an amine IV.



IV

That is, by some means the para-methoxy group had been replaced by hydrogen. This phenomenon is by no means new (18,19).

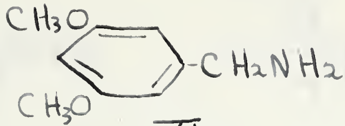
It was therefore suggested that the reduction of V with various



V

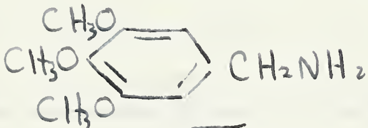
reducing agents be studied. The reducing agents selected were: (1) sodium in absolute ethanol, (2) sodium amalgam, (3) lithium aluminum hydride, (4) low pressure hydrogenation.

Of these four reducing agents, it was found that sodium in absolute ethanol was the only one in which the para-methoxy group was replaced by hydrogen. This reduction gave VI, isolated as the



VI

hydrochloride. The other three reducing agents gave the expected amine, VII.



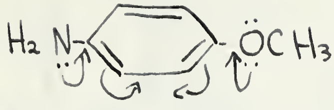
VII

E. Schwenk et al (20) found that treatment of VIII with

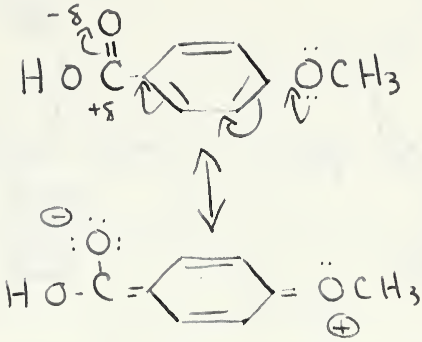
VIII

IX

Raney nickel in alkaline solution did not result in replacement of the para-methoxy group with hydrogen, but when the ortho, para directing amino group was replaced by a meta directing group, as in IX, hydrogenolysis to benzoic acid readily occured. To understand why hydrogenolysis occurs in one case and not in another, one must consider the resonance structures for the two molecules.

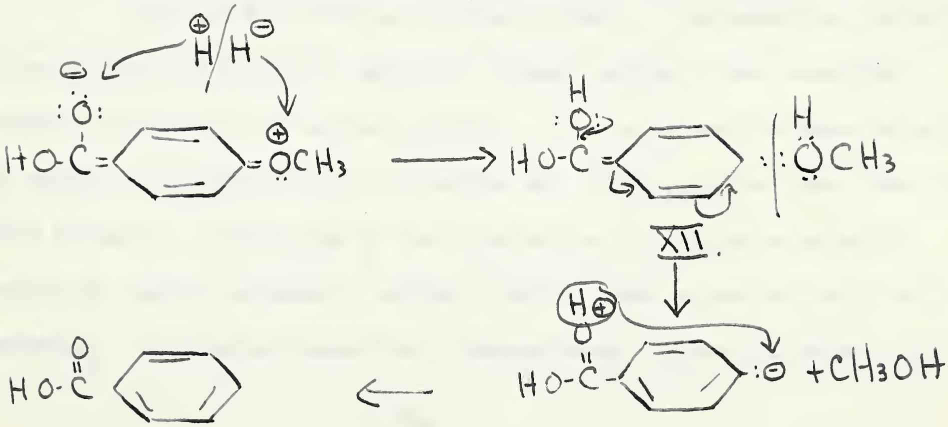


X



XI

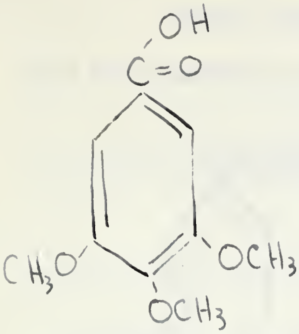
In X, the resonance effects of the two groups, which are both ortho, para directing, are opposed. Thus the bond between the methoxy group and the aromatic nucleus is going to be more aliphatic in character than that in XI in which the two groups are in conjugation. Thus, hydrogenolysis should occur more readily in XI because we can have an attack at the electronically deficient oxygen atom to give XII



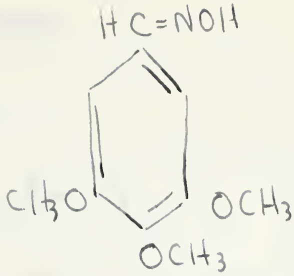
XII.

which on rearrangement could split out a molecule of methanol.

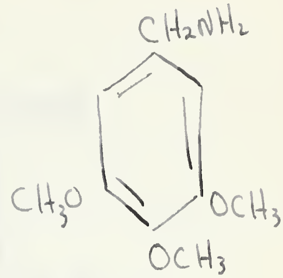
The same workers also noted that when XIII was treated in the



XIII



XIV

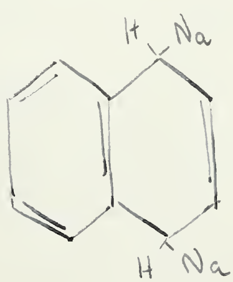


XV

same manner it was recovered unchanged. This is probably due to the steric inhibition of resonance by the two adjacent methoxy groups. This would make the bond between the para-methoxy group more aliphatic in nature than that in para-methoxybenzoic acid, and thus would be harder to split.

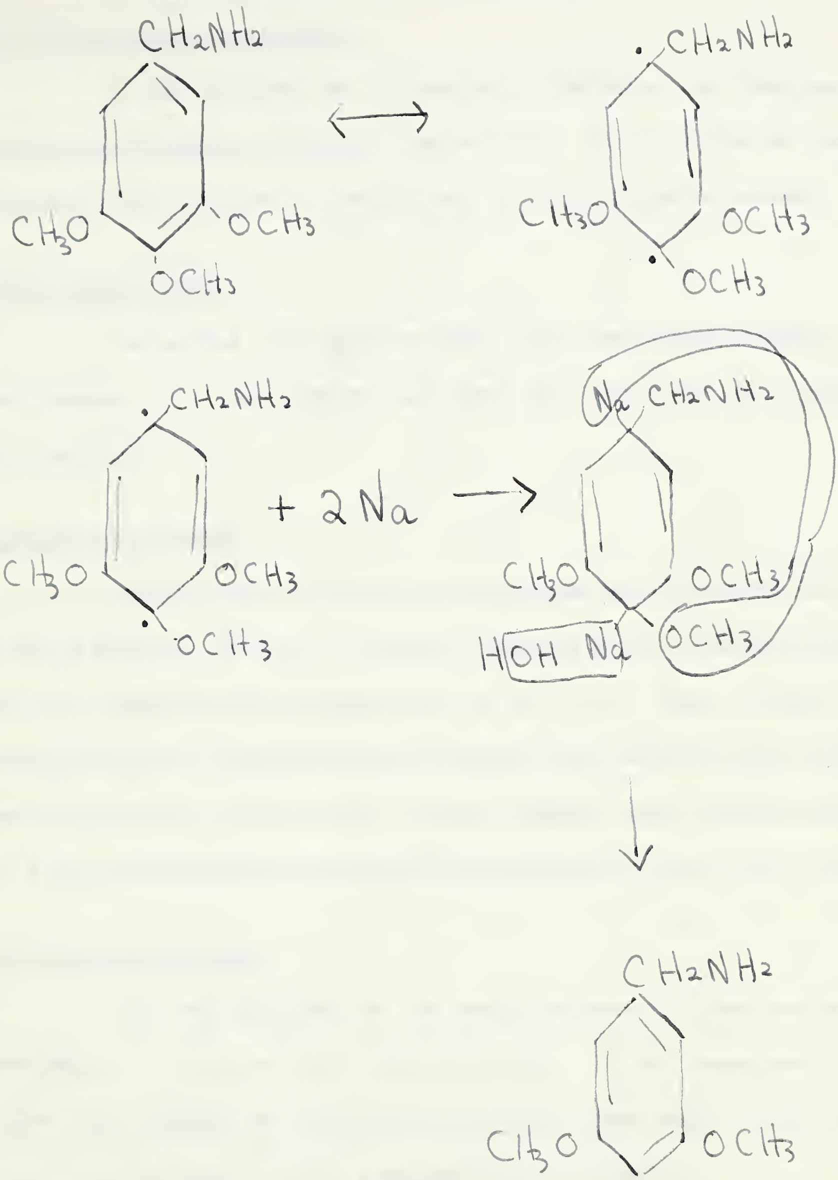
This should explain why the para-methoxy group is not replaced by hydrogen in XIV or XV when treated with sodium amalgam, lithium aluminum hydride, or low pressure hydrogenation.

The fact that the para-methoxy group is replaced when reduction takes place with sodium in absolute ethanol suggests that something besides hydrogenolysis may be occuring. In the Bouveault-Blane reduction of esters to alcohols (21) with sodium and alcohol it has been shown that "The formation of hydrogen by the interaction of sodium and alcohol serves no useful purpose." Sodium, itself, takes an actual part in the reaction. It is also known that intermediates such as XVI exist (22).



XVI

Taking these facts into consideration, the following mechanism for the reaction is proposed.



EXPERIMENTAL

All melting points are uncorrected.

3,4,5-Trimethoxybenzaldehyde

It was prepared by the method of McFadyen and Stephens as outlined by Buchanan, Cook and Loudon (4d). Distillation at reduced pressure gave a product of sufficient purity for further steps.

3-Nitroacetophenone

The method developed by Cobb (23) involving nitration of acetophenone at a temperature less than -20° was found to be most satisfactory.

3-Aminoacetophenone

Thirty grams of 3-nitroacetophenone was dissolved in 200 ml. of ethyl acetate, 0.05 g. of Adam's platinum oxide catalyst was added, and then submitted to hydrogenation at 50 p.s.i. When a drop in pressure corresponding to theoretical was obtained the solution was filtered free of platinum and the ethyl acetate removed under reduced pressure. The 3-aminoacetophenone obtained was practically pure, m.p. 93-94.5°.

3-Hydroxyacetophenone

This was prepared by the usual method of diazotization and hydrolysis of the resulting diazonium salt. It was necessary to purify the material by recrystallizing twice from water using Norit if it is to be used for the preparation of chalcones.

3-Methoxyacetophenone

Thirty grams of 3-hydroxyacetophenone was dissolved in 150 ml. of 30% sodium hydroxide solution. After cooling to 15°, 30 ml. of dimethylsulfate was added slowly with stirring over a period of 20

minutes. Thirty ml. more of dimethylsulfate was then added over a period of 10 minutes. The solution was then refluxed for two hours, cooled, and extracted with benzene. The 3-methoxyacetophenone was obtained by distillation at reduced pressure (b.p. 160°/3 mm.)

3,3',4,5-Tetramethoxychalcone

A. To a solution of 1.96 g. of 3,4,5-trimethoxybenzaldehyde and 1.5 g. of 3-methoxyacetophenone in 10 ml. methanol in the cold was added a solution of 0.2 g. of sodium in 5 ml. of methanol. The solution was allowed to attain room temperature and then let stand. After approximately two weeks a small amount of white material precipitated out of solution. Recrystallization from ethanol afforded some white fluffy crystals, m.p. 170-171°. This was obviously not the expected chalcone. The analysis, as reported by another worker (10a), agreed within experimental error with that of the chalcone or its higher condensation products.

B. Three grams of 3-methoxyacetophenone and 3.9 g. of 3,4,5-trimethoxybenzaldehyde were dissolved in 30 ml. of ethanol containing 0.5 g. of sodium hydroxide. Water was added to the cloud point (15 ml.) and the mixture was then shaken for two hours after which it was allowed to stand overnight. A yellow oil settled out which would not solidify. The material was distilled at reduced pressure (160°/3 cm.) and yielded an oil which when recrystallized from ethanol afforded 2.5 g. of white material, m.p. 140-141°.

3,4,5-Trimethoxy-3'-hydroxychalcone

Three grams of 3-hydroxyacetophenone and 4.3 g. of 3,4,5-trimethoxybenzaldehyde were dissolved in 25 ml. boiling methanol. This solution was cooled in ice until a white, flocculent precipitate

of 3,4,5-Trimethoxybenzaldehyde settles out, then 25 ml. of an ice-cooled solution of potassium hydroxide (30%) in methanol was added. The mixture was allowed to stand for six hours with occasional shaking. The bulk of the methanol was then removed at reduced pressure leaving a thick orange paste which was dissolved in water and extracted with ether to remove any unreacted aldehyde. Acidification of the aqueous layer with dilute hydrochloric acid, while cooling internally with ice, yielded a yellow oil which solidified almost immediately. Recrystallization from ethanol afforded 6.0 g. (87%) of beautiful yellow material, m.p. 173-174°.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.8%; H, 5.77%

Found: C, 68.3%; H, 5.94%

3,4,5-Trimethoxy-3'-hydroxyhydrochalcone

Fifteen grams of the preceding chalcone was dissolved in boiling methanol and reduced at 50 p.s.i. in the low-pressure hydrogenation apparatus using Adam's platinum oxide catalyst (0.05 g.). The platinum was filtered off and the methanol distilled off under vacuum leaving a faintly yellow solid. Recrystallization from ethanol afforded 13.5 g. (90%) of white material, m.p. 140-140.5°.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.3%; H, 6.37%.

Found: C, 68.4%; H, 6.49%

3,3',4,5-Tetramethoxyhydrochalcone

Ten grams of the preceding hydrochalcone and 4 g. of sodium hydroxide were dissolved in water. Four grams (3 ml.) of dimethylsulfate was added slowly, with stirring which was continued for 15 minutes. A further 3 ml. of dimethylsulfate was then added and after stirring 10 minutes the mixture was refluxed for one hour. On cooling

the brown oil produced slowly solidified and was then filtered off. Recrystallization from ethanol afforded an 80% yield of white plates, m.p. 69-70°.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 68.8%; H, 5.80%

Found: C, 68.5%; H, 5.75%

1-(3-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine hydrochloride

Eight grams of Ingersoll's (24) formate-formamide reagent and 5.5 g. of the preceding hydrochalcone were heated in an oil bath at 165-185° for five hours. Twenty-five ml. of 12N hydrochloric acid and 25 ml. of ethanol were then added and the mixture refluxed for one hour. The mixture was then made basic with sodium hydroxide and extracted with ether. The ether solution was dried with anhydrous sodium sulfate, filtered free of sodium sulfate, then dry hydrogen chloride passed through. An oil separated out which when treated with absolute ethanol solidified. Recrystallization from commercial absolute ethanol afforded 3 g. (56%) of a white solid, m.p. 195-196°.

Anal. Calcd. for $C_{19}H_{26}O_4NCl$: Cl, 9.60%. Found: 9.31%

N-Acetyl-1-(3-methoxyphenyl-3-(3,4,5-trimethoxyphenyl)-propylamine

To a suspension of 4.5 g. of the hydrochloride in water at about 60° was added 1.3 ml. of acetic anhydride. While stirring, 1.5 g. of sodium acetate was added immediately. A viscous oil separated out on the walls of the flask. Repeated recrystallization from dilute ethanol afforded a small amount of a white, fluffy solid, m.p. 92-93°.

Anal. Calcd. for $C_{21}H_{27}O_5N$: C, 67.5%; H, 7.29%

Found: C, 67.6%; H, 7.53%

3,4,5-Trimethoxy-3-hydroxyhydrochalcone oxime

Twelve grams of 3,4,5-trimethoxy-3'-hydroxyhydrochalcone and 3.3 g. of hydroxylamine hydrochloride were dissolved in 27 ml. of commercial absolute ethanol and 27 ml. of pyridine and refluxed for five hours. The solution was poured on ice and the oil which settled out solidified on standing. Recrystallization from dilute ethanol afforded 120 g. of white material, m.p. 131-131.5°.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.3%; H, 6.39%

Found: C, 65.3%; H, 6.76%

1-(3-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine

A. By sodium amalgam reduction.

Three grams of the preceding oxime was dissolved in 30 ml. of warm ethanol and treated with 150 g. of 3.5% sodium amalgam, added in small portions over a one hour period. Fifteen ml. of glacial acetic acid was added at such a rate so as to keep the solution just acid to litmus. When sodium acetate separated out, enough water was added to keep it in solution. After standing two hours further the mercury was separated, the solution was filtered, and to the filtrate ammonium hydroxide was added. A brown solid separated out which after repeated recrystallization from alcohol-benzene yielded a small amount of a white solid, m.p. 193-194°.

Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.0%; H, 7.43%

Found: C, 68.1%; H, 7.30%.

B. By high pressure hydrogenation.

Three grams of the oxime and 1 g. of Raney Nickel were suspended in 20 ml. of ethanol. Reduction was carried out at 85° and 1000 p.s.i. for one hour. The product was then extracted from the Raney Nickel with boiling ethanol. The ethanol solution was

boiled down to a small volume and allowed to cool. A white solid separated out, m.p. 193-194°.

Yield: 80%. Mixed m.p. with material from the sodium amalgam reduction, m.p. 193-194°.

N-Acetyl-1-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine

1-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine hydrochloride was prepared according to the directions of Christiansen (10a). The hydrochloride was then acetylated as before in the preparation of N-acetyl-1-(3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine. A white, fluffy solid was obtained, m.p. 85.5-86.5°.

Anal. Calcd. for $C_{21}H_{27}O_5N$: C, 67.5%; H, 7.29%.

Found: C, 67.8%; H, 7.60%.

3,4,5-Trimethoxy-4'-hydroxychalcone

This chalcone was prepared in the same manner as 3,4,5-trimethoxy-3'-hydroxychalcone from 3,4,5-trimethoxybenzaldehyde and 4-hydroxyacetophenone in 15% potassium hydroxide in methanol. Recrystallization from ethanol afforded beautiful yellow needles, m.p. 235-236°.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.8%; H, 5.77%.

Found: C, 69.0%; H, 6.28%.

3,4,5-Trimethoxy-4'-hydroxyhydrochalcone

It was prepared from the preceding chalcone by low-pressure hydrogenation. Recrystallization from dilute ethanol afforded beautiful white plates, m.p. 156-157°.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.3%; H, 6.37%.

Found: C, 67.9%; H, 6.51%.

3,4,5-Trimethoxy-4'-hydroxyhydrochalcone oxime

It was prepared from the preceding hydrochalcone and hydroxylamine hydrochloride, refluxed in a mixture of absolute ethanol and pyridine, as before. Recrystallization from dilute ethanol afforded beautiful white plates, m.p. 156-157°.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.3%; H, 6.39%.

Found: C, 65.7%; H, 6.30%.

3,4,5-Trimethoxybenzaldoxime

Twenty grams of 3,4,5-trimethoxybenzaldehyde and 7.5 g. of hydroxylamine hydrochloride were dissolved in 60 ml. of pyridine and 60 ml. of commercial absolute ethanol. After refluxing for five hours the solution was poured on ice to give an oil which soon solidified (19 g.), m.p. 85-87°. Recrystallization from benzene afforded 16.5 g. of beautiful white needles, m.p. 83-84°.

Reduction by Sodium in Absolute Ethanol

To a refluxing solution of 2 g. of 3,4,5-trimethoxybenzaldoxime in 55 ml. of commercial absolute ethanol was added 6 g. of sodium in small pieces on the end of pointed glass rods. The solution was then cooled and excess water added. The amine was extracted with ether, the ether dried with potassium hydroxide pellets followed by anhydrous sodium sulfate, and dry hydrogen chloride passed through the ether solution. A white solid separated out, m.p. 198-200° (1 g.). Recrystallization from ethanol-ether afforded fine white needles, m.p. 199-200°.

Anal. Calcd. for $C_9H_{14}NCl$: Cl, 17.4%. Found: Cl, 16.8%.

Reduction by Sodium Amalgam

To a solution of 2 g. of 3,4,5-trimethoxybenzaldoxime in 30 ml. of ethanol was added in small portions over the period of one hour, 105 g. of 4% sodium amalgam. Fifteen ml. of glacial acetic acid was added over this period of time at such a rate so as to keep the solution slightly acidic. When all the sodium amalgam was added the solution was allowed to stand one hour. The mercury was then separated and the solution made basic. Excess water was added and the amine was extracted with ether. The ether solution of the amine was treated as before and afforded 1.55 g. of a white solid, m.p. 215-217°. Recrystallization from ethanol-ether afforded beautiful white needles, m.p. 216-217°.

Anal. Calcd. for $C_{10}H_{16}NCl$: Cl, 15.2%. Found: Cl, 15.7%.

Reduction by Lithium Aluminum Hydride

Two grams of oxime dissolved in 35 ml. of anhydrous ether is added slowly to 1.4 g. of lithium aluminum hydride in 100 ml. of ether at such a rate so as to keep the solution refluxing. The solution was refluxed further for three hours then, very cautiously, water was added to destroy excess lithium aluminum hydride. Concentrated sodium hydroxide solution was added to dissolve aluminum hydroxide formed then the solution was extracted with ether. The ether was treated as before and afforded 1 g. of white material, m.p. 215-217°. Recrystallization from ethanol-ether afforded white needles, m.p. 216-217°. Mixed m.p. with material from sodium amalgam reduction gave no depression.

Reduction by Low Pressure Hydrogenation

Fifteen grams (0.0071 moles) of oxime was dissolved in 25 ml. of ethanol containing 0.021 moles of hydrogen chloride. This was shaken at 50 p.s.i. in the low pressure hydrogenation apparatus for six hours using Adam's platinum oxide catalyst (0.05 g.). The platinum was filtered off and the ethanol removed in vacuo. The residue was dissolved in ether and the ether treated as before to give a white hydrochloride with m.p. 140-170°. Repeated recrystallization from ethanol-ether gave a small amount of material which softens at 205° and completely melts at 215°. Mixed m.p. with material from sodium in ethanol reduction, softens at 195°, melts at 205°. Mixed m.p. with material from lithium aluminum hydride reduction, softens at 210°, melts at 215°.

1. H. Lettre and H. Fernholz, Z. Physiol. Chem., 278, 175 (1943).

2. R.J. Ludford, J. Natl. Cancer Inst., 6, 89 (1945).

3. A. Windaus, Ann. 439, 59 (1924).

4. (a) A. Cohen, J.W. Cook and E.M.F. Roe, J. Chem. Soc., 194 (1940).

(b) J.W. Cook, Walter Graham, A. Cohen, R.W. Lapsley and C.A. Lawrence, ibid., 322 (1944).

(c) G.L. Buchanan, J.W. Cook and J.D. Loudon, ibid., 325 (1944).

(d) Norman Barton, J.W. Cook and J.D. Loudon, ibid., 176 (1945).

(e) J.W. Cook, G.T. Dickson and J.D. Loudon, ibid., 746 (1947).

5. H. Rapoport, A.R. Williams and M.E. Cisney, J. Am. Chem. Soc., 72, 3324 (1950).

6. M.J.S. Dewar, Nature, 155 (1945).

7. F. Santavy, C.R. Soc. Biol., 140, 932 (1946).

H.R.V. Arnstein, D.S. Tarbell, H.T. Huang and G.P. Scott, J. Am. Chem. Soc., 70, 1669 (1948).

8. H. Lettre, M. Albrecht and H. Fernholz, Naturwissenshaften, 29, 390 (1941).

9. J.L. Hartwell and S.R.L. Kornberg, J. Am. Chem. Soc., 67, 1606 (1945).

10. (a) R.G. Christiansen, Master's Thesis, University of Alberta Library, (1948).

(b) R.R. Brown, Master's Thesis, University of Alberta Library, (1950).

11. Private communication from J.L. Hartwell, National Cancer Institute, Bethesda, Maryland.

12. (a) S.V. Kostanecki and G. Rossbach, Ber. 29, 1488-94 (1896).

(b) D.B. Andrews and R. Connor, J. Am. Chem. Soc., 57, 895 (1935).

13. Private communication from F.C. Chubb, University of Alberta, Edmonton.

14. A.V. Wacek and I. Morghen, Ber. 70B, 183-9 (1937).

15. Organic Reactions, Vol. V, p. 311.

16. R. Paul, Bull. Soc. Chim. (5), 4, 1121-5 (1937).

17. Private communication from A. Nichon and R.R. Brown, University of Alberta.

18. H. Thoms and W. Siebeling, Ber. 44, 2134 (1911).

19. F.W. Semler, ibid., 41, 1768, 2556 (1908).

20. E. Schwenk, D. Papa, B. Whitman, H. Ginsberg, J. Org. Chem., 9, 1-8 (1944).

21. R.C. Fuson, "Advanced Organic Chemistry", John Wiley and Sons, New York (1950), p.366.

22. W. Huckel and H. Bretschneider, Ann. 540, 157-89 (1939).

23. E.C. Cobb, Proc. S. Dakota Acad. Sci., 25, 64-5 (1945).

24. A.W. Ingersoll, J.H. Brown, C.K. Kim, W.D. Beauchamp, and G. Jennings, J. Am. Chem. Soc, 58, 1808 (1936).